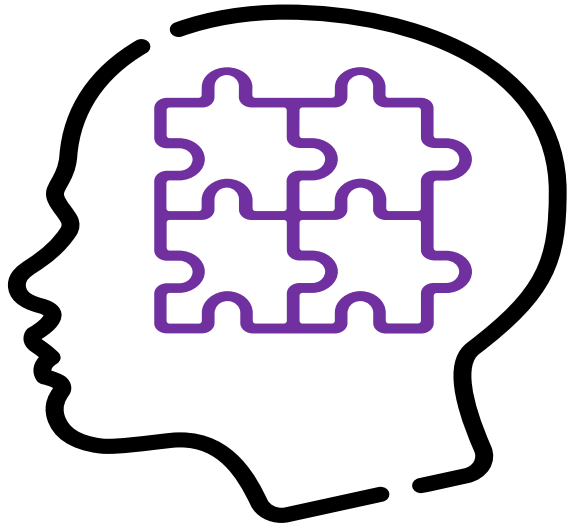
Phramongkutklao Comprehensive
Pediatric Epilepsy Center of Excellence

Integration • Passion • Wisdom

Cutting-edge Treatment in Status Epilepticus



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Outline

- What is the **new** treatment of Pediatric Status Epilepticus?
  - Acute initial treatment
    - BDZ in the out-of-hospital setting
  - Treatment of established SE
    - Evidence-based RCTs
  - Treatment of RSE and Super-Refractory SE
    - Novel drugs
    - Alternative treatments

Pediatric status epilepticus PSE

- A severe condition with high morbidity and mortality
- One in 50 children with epilepsy -> develop SE per year
- Peak incidence under 2 years of age
- A convulsive episode in the setting of a febrile disease is most common

Lancet Child Adolesc Health 2020

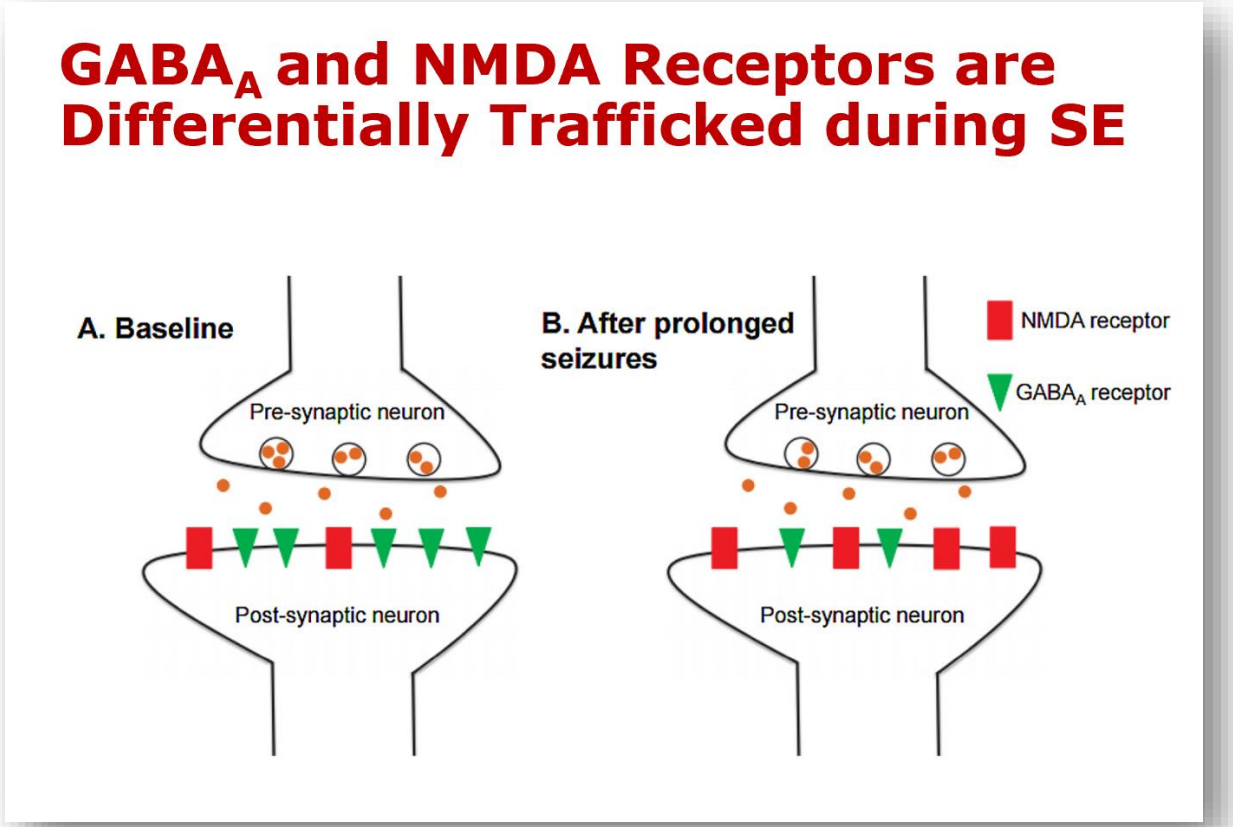
A definition and classification of status epilepticus Report of the ILAE Task Force (2015)

Type of SE	Operational dimension 1 Time (t1), Sz likely to be prolonged leading to continuous sz activity	Operational dimension 2 Time (t2), Sz may cause long term consequences
Tonic-clonic SE	5 min	30 min
Focal SE w/impaired consciousness	10 min	> 60 min
Absence SE	10-15 min	Unknown

Epilepsia 2015

Pathophysiology

- Imbalance of the inhibitory activity of the neurotransmitter **γ–amino butyric acid (GABA)** and the excitatory neurotransmitter glutamate (Glu)
- Subcellular changes with **internalization of postsynaptic GABA-A receptors**, accumulation and **externalization of excitatory NMDA-receptors**, change in subunits composition of **AMPAR**, changes in chloride homeostasis, etc.



M Gaínza-Lein, et al Seizure 2019

Early SE: Benzodiazepines First Line Therapy

	Diazepam	Midazolam	Lorazepam
Route	IV, PR	IV, IM, IN, buccal	IV
Max dose	10 mg for IV 20 mg for PR	10 mg	4 mg
Onset of action	1-3 min	3-5 min	6-10 min
Duration of action	15-30 min	15-30 min	12- 24 hr
Disadvantages	Prolonged sedation Respiratory depression	Short half-life Risk of seizure relapse	Rapid tolerance
Advantages	Rapid onset Widespread availability	Water soluble	Less lipid soluble

Sing A, et al. CNS Drugs 2020

An intranasal diazepam rescue therapy

- Out-of-hospital treatment
- Benzodiazepine rescue therapy should allow for quick and easy use by nonmedical persons
- Doses: 5, 10, 15, 20 mg
- Patient age: ≥ 6 years (USA FDA-approved)
- AEs in ≥4%: somnolence, headache, nasal discomfort

Cloyd J, et al. Epilepsia. January 2021

An intranasal diazepam rescue therapy

- In a Phase 1 study, absolute bioavailability of the diazepam nasal spray was 97% compared with intravenous diazepam

- The nasal spray demonstrated less variability in bioavailability than rectal gel (42%–66% for diazepam nasal spray compared with 87%–172% for rectal gel)

Cloyd J, et al. Epilepsia. January 2021

Treatment of established SE

Randomized control trial in CSE: EcLiPSE, ConSEPT and ESETT

Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial

*Mark D Lyttle, Naomi E A Rainford, Carrol Gamble, Shrouk Messahel, Amy Humphreys, Helen Hickey, Kerry Woolfall, Louise Roper, Joanne Noblet, Elizabeth D Lee, Sarah Potter, Paul Tate, Anand Iyer, Vicki Evans, Richard E Appleton, with support of Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative**

Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial

Stuart R Dalziel, Meredith L Borland, Jeremy Furyk, Megan Bonisch, Jocelyn Neutze, Susan Donath, Kate L Francis, Cynthia Sharpe, A Simon Harvey, Andrew Davidson, Simon Craig, Natalie Phillips, Shane George, Arjun Rao, Nicholas Cheng, Michael Zhang, Amit Kochar, Christine Brabyn, Ed Oakley, Franz E Babl, on behalf of the PREDICT research network

Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial

James M Chamberlain, Jaideep Kapur, Shlomo Shinnar, Jordan Elm, Maija Holsti, Lynn Babcock, Alex Rogers, William Barsan, James Cloyd, Daniel Lowenstein, Thomas P Bleck, Robin Conwit, Caitlyn Meinzer, Hannah Cock, Nathan B Fountain, Ellen Underwood, Jason T Connor, Robert Silbergleit, for the Neurological Emergencies Treatment Trials and the Pediatric Emergency Care Applied Research Network investigators†*

Lyttle MD, Lancet 2019, Dalziel SR, Lancet 2019, Kapur J, NEJM 2019, Chamrberlain JM, Lancet 2020

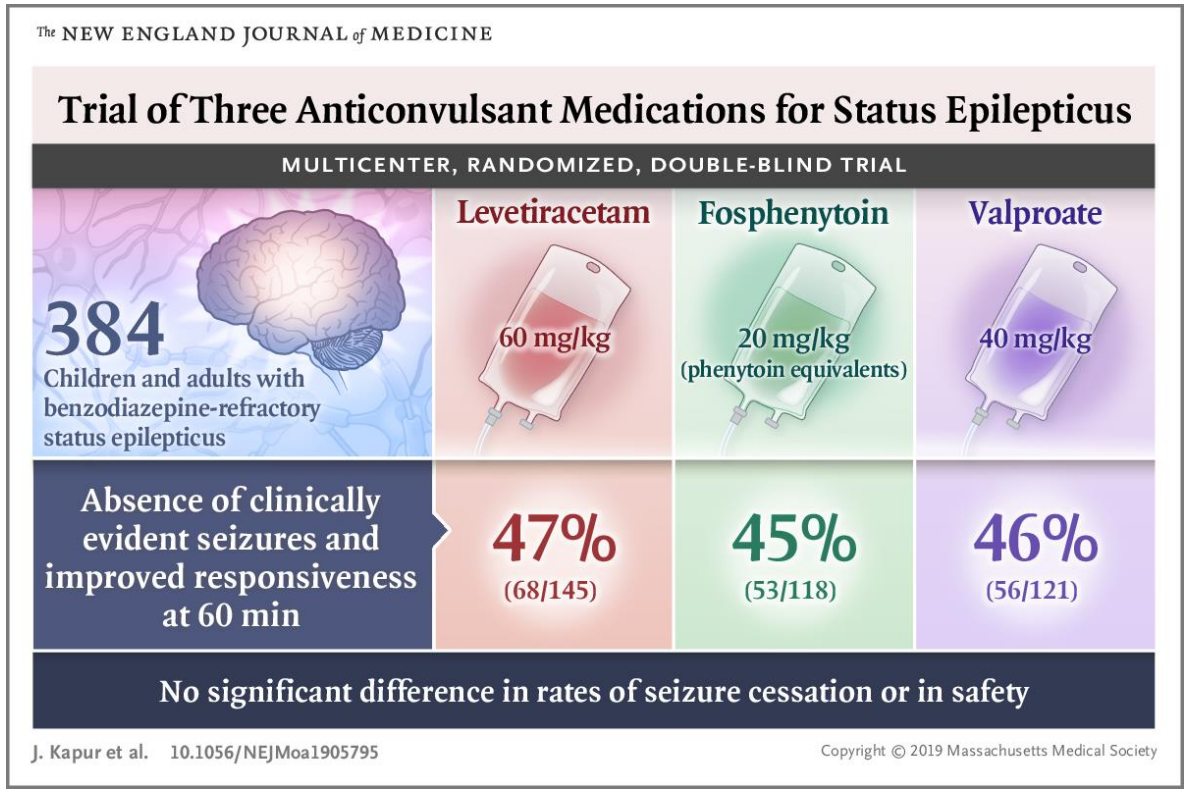
EcLiPSE and ConSEPT Trial

	EcLiPSE (n = 296)	ConSEPT (n = 233)
Patients	Age 6 mo – 18 years	Age 3 mo – 16 years
Study	Multicenter, RCT, UK	Multicenter, RCT, AUS + NZ
Intervention	PHT 20 mg/kg over 20 min vs LEV 40 mg/kg over 5 min	
Outcome	Time to randomization to cessation of CSE	Clinical cessation of seizure activity 5 min after infusion end
Resutls	Median time to stop: PHT 45 min vs LEV 35 min	PHT (60%) vs LEV (50%)
Conclusion	LEV is not superior	No significant difference

Courtesy of Dr. Kullasate S.

Lyttle MD, Lancet 2019, Dalziel SR, Lancet 2019

ESETT
(Established Status Epilepticus Treatment Trial)



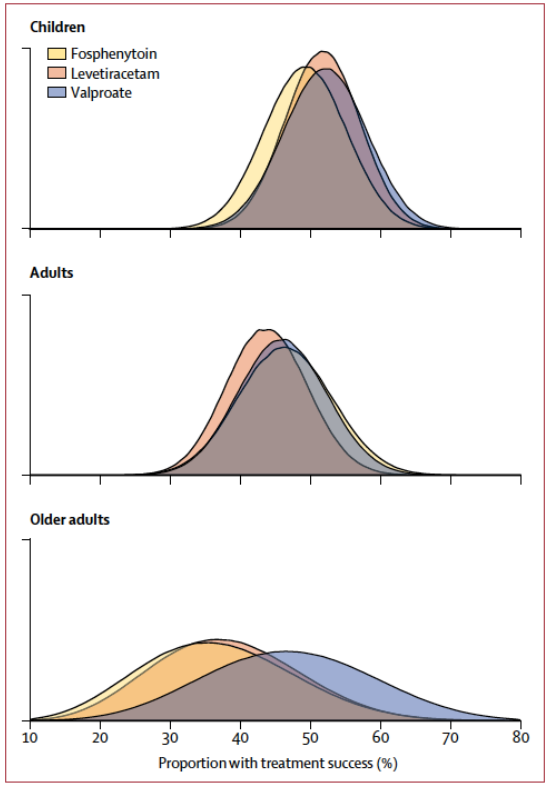


Figure 2: Posterior probabilities of success by age and treatment groups for the primary outcome

Children > 2 yo, GTC > 5 min and continue Sz after adequate doses of BDZ
LEV 60 mg/kg (max 4500 mg)
fPHT 20 mg/kg (max 1500 mg)
VPA 40 mg/kg (max 3000 mg)

Kapur J, NEJM 2019, Chamrberlain JM, Lancet 2020

Refractory and Super-refractory SE

- RSE is seen in 23–44% of patients with CSE
- Definition:
  - **RSE** is continuous seizure activity not controlled by first-line and second-line ASMs[1]
  - **Super-refractory SE** is defined as status epilepticus not controlled by third-line agents[2]
    continues for 24 hours or longer after anesthesia is administered[3]
- There is **no clear evidence** to direct therapy in this phase
- There is ongoing debate regrading risks/benefits of generalized anesthesia for RSE

[1]Rossetti AO et al. Lancet Neurol 2011; 10(10):922–930.
[2]Reznik ME, J Clin Med 2016; 5(5):pii:E54.
[3]Kantanen AM, Epilepsy Behav 2015; 49:131–134.

Drug	Loading Dose	Maintenance Dose	Level	AE, Interaction
Third-Line Agents				
Midazolam	0.2 mg/kg IV every 5 min until seizures controlled (max 2mg/kg)	0.1-2.0 mg/kg/h CIV	NA, titrate to EEG suppression	Sedation, respiratory depression, hypotension
Propofol	2 mh/kg IV every 5 min until seizures controlled max 10 mg/kg	2-15 mg/kg/h CIV (limit to 5 mg/kg/h) for treatment >48 h)	NA, titrated to EEG suppression	Sedation, respiratory depression, hypotension **Propofol infusion syndrome**
Pentobarbital	5 mg/kg IV up to 50 mg/min every 5 min until seizures controlled	1-10 mg/kg/hr CIV	NA, titrated to EEG suppression	Sedation, respiratory depression, hypotension, ileus metabolic acidosisthrombocytopenia, immunosuppression
Ketamine	1.5 mg/kg IV every 5 min until seizure conbtrolled max dose 4.5 mg/kg	1.2-7.5 mh/kg/hr CIV	NA, titrated to EEG suppression	Hypertension, possible raise in ICP

Hirsch and Gaspard, 2013

Ketamine

- 9 case series (total 260 cases of SRSE)
- The first multicenter, randomized controlled, open label study for RSE in children is on-going in Italy
- Early use of Ketamine for SE, mainly in combination with other drugs in animal with promissing result
- Age: 1.3-86 years
- Dose up to 10.5 mg/kg/hr
- Response rate: 32-100%
- Earlier use tended to be associated with better responses
- Few AE (cardiac arryhmia)
- No observable effect on ICP
- Cardio-circulatory supportive effects often noted

Rosati et al., 2012; Gaspard et al., 2013; Synowiec et al., 2013; Sabharwal et al., 2015; Basha et al.,2015; Hofter et al.,2016 Santoro et al., 2019; Dericioglu et al., 2020; Alkhachroum et al., 2020, Rosati et al., 2016

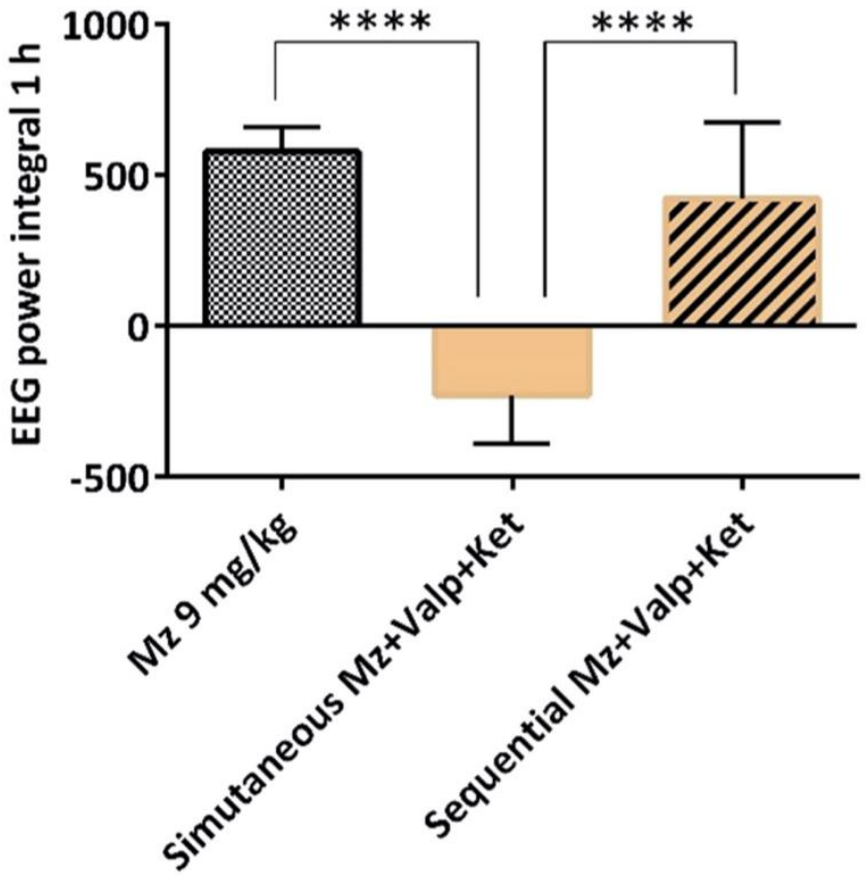
Compilation of animal and human studies about early polytherapy in SE

Study	Subjects	Compared alternatives	Outcome	Results	EP
Martin and Kapur, 2008	L-P rat model (adult male SD rats)	DZP-KET vs DZP vs KET vs placebo	SE termination measured by EEG activity for at least 5h (termination when EEG turned to baseline or irregular spikes without recurrence of seizures) and behavior observation	DZP-KET the most effective	+
Wasterlain et al., 2011 Niquet et al., 2017	Severe L-P rat model (male Wistar rat)	DZP-KET-VPA (low dose) vs each drug alone (even high doses)	Reducing several parameters of SE severity, based on EEG (EEG power integral, Hjorth function, spikes, seizures –number, cumulative time, composite-, amplitude, time to normality, SE duration, etc). 24h EEG.	Triple therapy more effective than monotherapy without adding side effects	+
Sreenath et al., 2010	178 children GCSE	LZP vs DZP-PHT. Randomized	Seizure activity termination (based on clinical activity after 10 min, and no recurrence in 18h)	No differences	-
Aranda et al., 2010	Adults. 101 episodes GCSE	Observational study (evaluation professional practice).	Use of AEDs. Seizure activity termination (after 20 min, and no recurrence in 1h, based on clinical activity +/-EEG).	DZP/CZP-FPHT better than BZD alone	+
Navarro et al., 2016	203 adults GCSE	CZP-LEV vs CZP placebo. Randomized, double-blind, phase 3	Seizure activity termination (after 15 min).	Stop. No differences	-

*EP: early therapy, DZP: diazepam, KET: ketamine, CZP: Clonazepam

M Amengual-Gual et al. Seizure 2019

Simultaneous Polytherapy was Far More Effective Than Sequential Therapy



Niquet et al., 2019

Refractory and Super-refractory SE

- In the absence of comparative studies, a combination therapy of no more than three ASMs is recommended
- Important Factors: the maximum tolerated dose, predictable pharmacokinetic profile, and adverse effects
- Published data (small series):
  - Levetiracetam (LEV)
  - Topiramate (TPM)
  - Pregabaline (PGB)
  - Lacosamide (LCM)
  - Perampanel (PER)

Gomes D, et al. Consensus protocol for the treatment of superrefractory status epilepticus. Acta Med Port. 2018;31(10):598–605.

Systematic review of the literature of Perampanel: Results

10 articles

A total of 69 episodes of SE occurring in 68 patients (aged 18 to 91 years).
The type and etiology of SE varied remarkably across studies.

Previous AEDs

The number of drugs used prior to PER ranged from 1 to 9.

Time before add PER

The time from SE onset to PER administration ranged from 9.25 h to 35 days.

Initial PER dose

The initial PER dose ranged from 2 to 32 mg.

% of SE cessation

The proportion of patients achieving clinical SE cessation varied from 17% to 100%.

Time of SE cessation

The time from PER administration to SE cessation ranged from 1 h to 4 weeks.

Brigo F, Lattanzi S, Rohracher A, Russo E, Meletti S, Grillo E, Trinka E. Perampanel in the treatment of status epilepticus: A systematic review of the literature. *Epilepsy & Behavior.* 2018;86:179—186.

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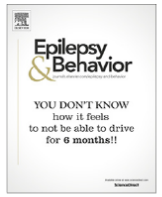

Efficacy of oral perampanel in status epilepticus and acute repetitive seizures in children at a tertiary care hospital in Thailand

Peeraya Wachiropathum [1], Charcrin Nabangchang [1], Napakjira Likasitthananon, Piradee Suwanpakdee *

Neurology Division, Department of Pediatrics, Phramongkutklao Hospital, Bangkok, Thailand

Dose of Perampanel.

Bodyweight (Kg)	Loading dose (mg)	Maintenance dose (mg)
≤10 kg	2	1
11–20 kg	4	2
21–30 kg	6	3
31–40 kg	8	4
≥41 kg	12	6

Results: The average loading and maintenance dose were 0.24 mg/kg/dose and 0.12 mg/kg/day, respectively.

- At 48 h, 8/15 patients (53.3%) became seizure free, one patient had seizure reduction of >75%, and three patients had seizure reduction of 25–50%.
- No serious side effects were observed.

Conclusion: **Oral perampanel may be potential treatment option for SE and ARS in children**

Peeraya W, et al, *Epilepsy & Behavior* 202

Lacosamide

- Introduced in 2008, enhanced slow inactivation of voltage-gated sodium channel
- Rapid spread in clinical practice due to its favorable pharmacological properties (minimal protein-binding/ drug interaction/ side effects)
- Highly soluble in water> intravenous formulation
- Accumulated uses for added-on treatment of SE since introduction of intravenous preparation in 2009

Hindawi
Neurology Research International
Volume 2018, Article ID 8432859, 5 pages
https://doi.org/10.1155/2018/8432859

Hindawi

Research Article

Effectiveness and Adverse Effect of Intravenous Lacosamide in Nonconvulsive Status Epilepticus and Acute Repetitive Seizures in Children

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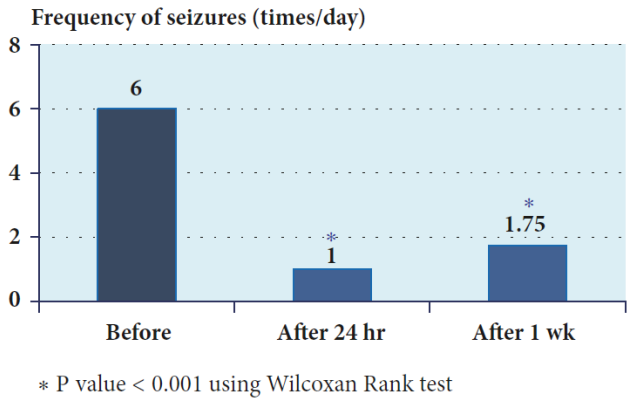


FIGURE 1: Comparison between seizure baseline 1 month before IV LCM and after IV LCM at 24 hours and 1 week.

- A prospective study in 18 years of age with NCSE or ARS
- Eleven patients with a median age of 11 years
- Average loading dose was 227 mg (8.3 mg/kg/dose) and average daily maintenance dose was 249 mg (4.6 mg/kg/dose).
- **All patients (100%) experienced a reduction in seizure frequency within 24 hours.**
- 8/11 patients (72.7%) experienced a reduction in seizure frequency of more than 50% by the end of the study

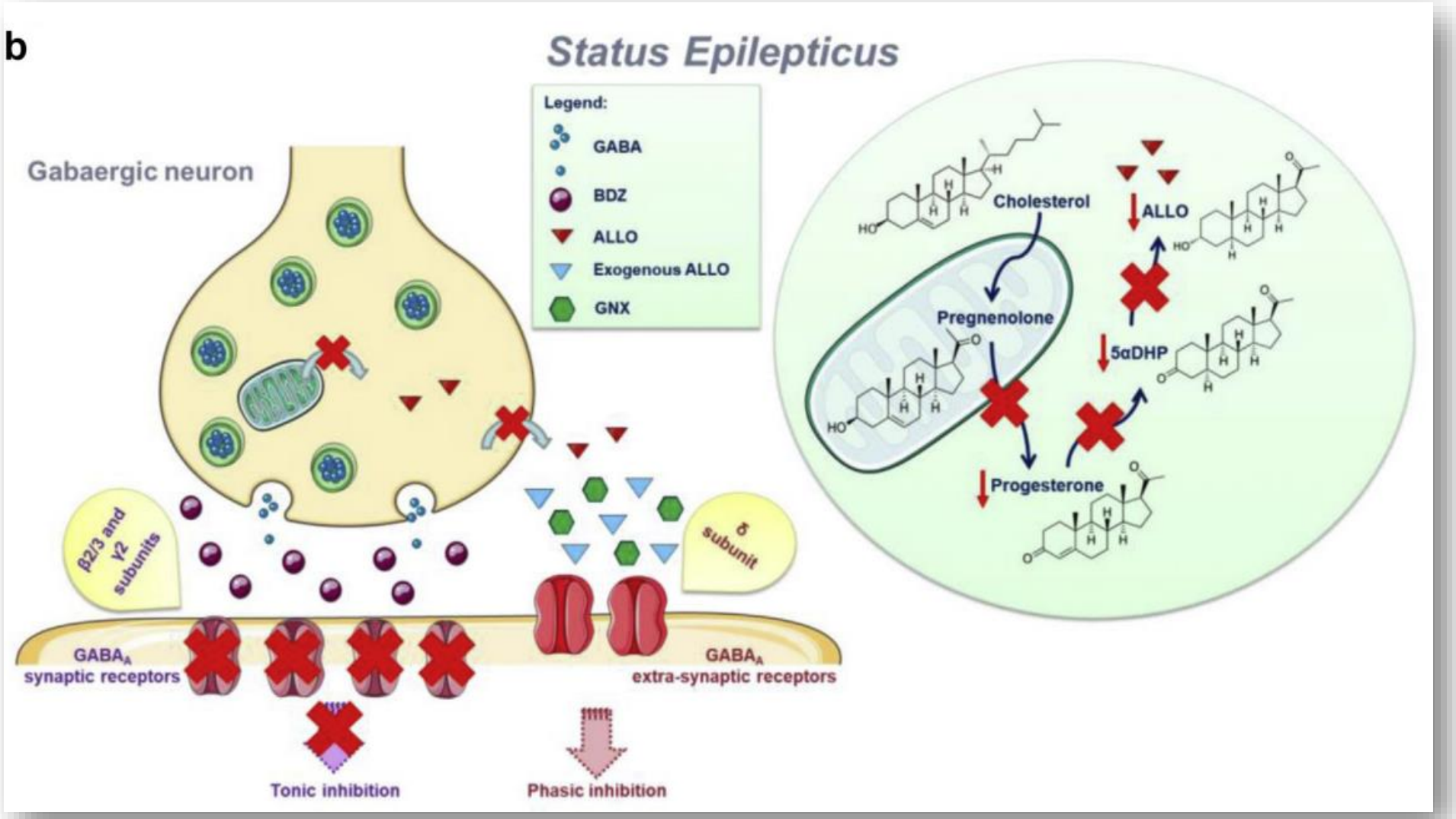
Ngampoopun M, et al. Neurol Res Int. 2018

Potentially New Strategy for Treatment of RSE and SRSE

- New treatement are needed for SE that is refractory to $GABA_A$ receptor modulating agent and NMDA receptor antagonist/ AMPA receptor antagonist are good candidate drugs
- $GABA_A$ receptor positive allosteric modulator neuroactive steroids can potentiate synaptic and extrasynaptic $GABA_A$ receptor
- Extrasynaptic $GABA_A$ receptors are not internalized or desensitized during SE
- **Allopregnanolone** a $GABA_A$ receptor positive allosteric modulator neuroactive steroids is an attractive target for treatment of BZD resistant SE

Courtesy of Dr. Charcrin N.

Neurosteroids



Gol M, et al. Current Opinion in Endocrine and Metabolic Research 2022

Super-Refractory SE: Neurosteroids

- Allopregnanolone

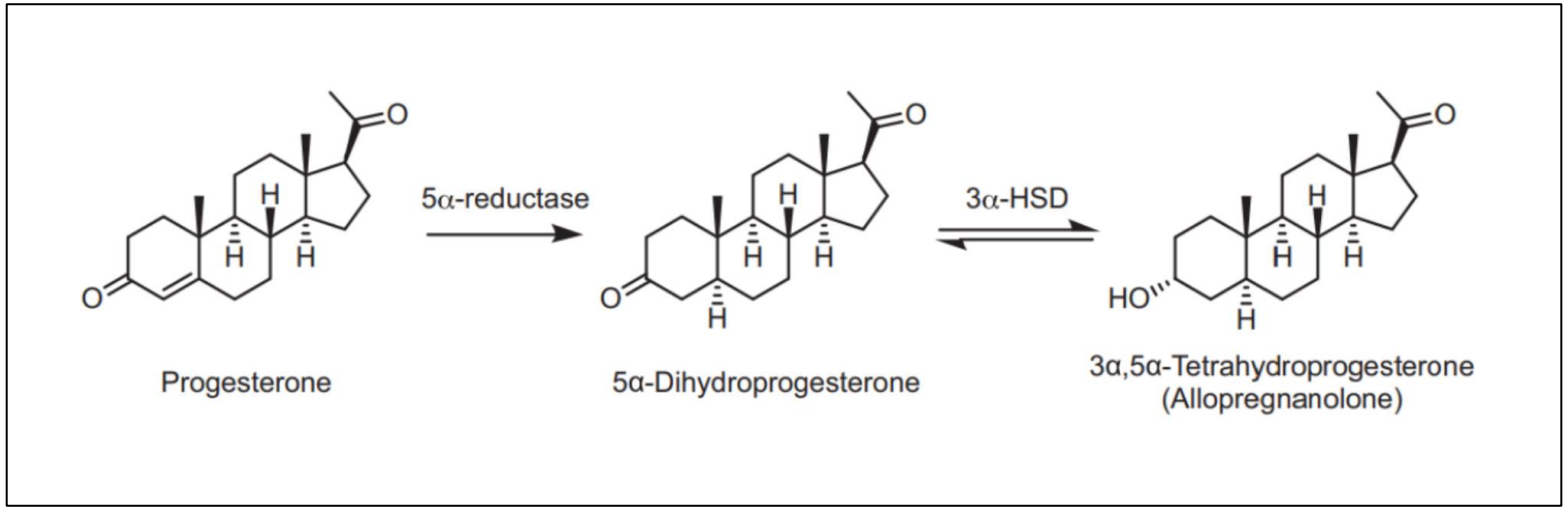
-Allosteric modurator of GABA (A) receptors

-Encouraging results in phase II (73% SRSE control)

-Phase III study negative (44% vs 43% SRSE control)

(Rosenthal et al., Ann Neurol 2017)

- Progesterone (Utrogestan® 200 mg)



Dichtel L.E. et. al., Neuropsychopharmacology. 2018

Drug Targeting The Immune System

- **Interleukin 1 receptor (Anakinra)**
  - The first drug targeting the immune system reported as effective in a patient with SRSE secondary to **FIRES (febrile infection-related epilepsy syndrome)**
  - A favorable response to IL-1 blockade has also been reported in a few patients with intractable epilepsy
  - In a preclinical study (using kainic acid-induced SE, diazepam-refractory, in a mouse model), the combination of IL-1 receptor antagonist with diazepam terminated established prolonged SE

Kenney-Jung DL, et al. Ann Neurol 2016

Case Report

Vagus Nerve Stimulation (VNS) in Super Refractory New Onset Refractory Status Epilepticus (NORSE)

Mohankumar Kurukumbi,[1] **James Leiphart**,[1] **Anam Asif**,[2] **and Jing Wang**[3]

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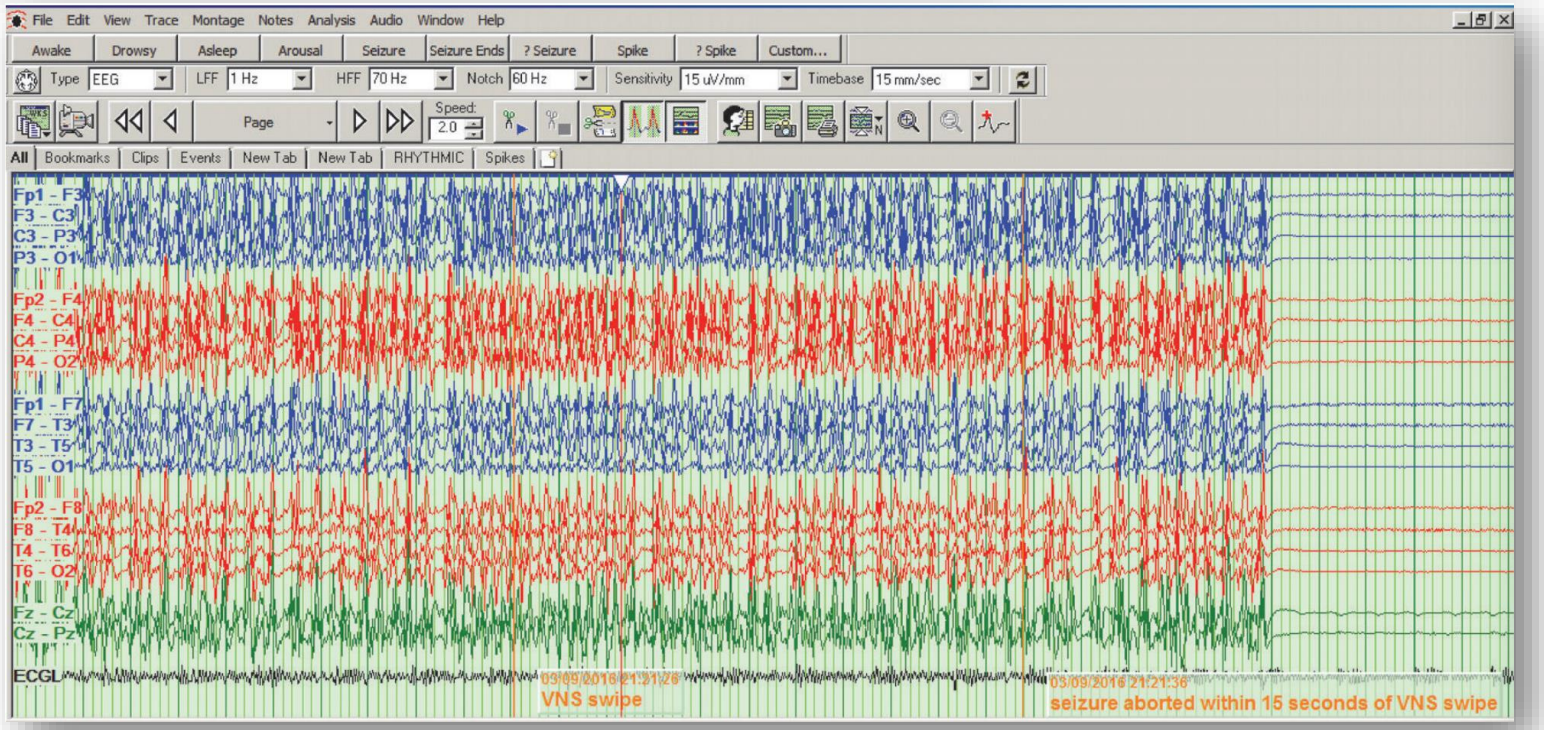
[2]*VCU School of Medicine, Inova Campus, Falls Church, VA, USA*
[3]*Department of Neurocritical Care, Inova Fairfax Hospital, Falls Church, VA, USA*

- A 25- year-old male with New Onset Refractory Status Epilepticus (NORSE)
- VNS was implanted on Day 8
- No SE or electrographic seizures were reported for seventy-two hours



Case Reports in Neurological Medicine 2019

Alternative treatments for RSE and SRSE

Treatment	Advantages	Disadvantages
Ketogenic diet	May help reduce excitotoxic damage	• Long time frame for treatment effect (1–2 weeks) • Adverse events: constipation, acidosis, hypoglycemia, hypercholesterolemia, pancreatitis
Hypothermia	Neuroprotective properties	Adverse events: coagulation disorders, hypotension, cardiac arrhythmia, infection, acid–base and electrolyte disorders, ileus, bowel ischemia • Interaction with anesthetics and ASD clearance
Epilepsy surgery	In selected cases, can lead to SE control or even seizure freedom	Difficult to detect SE focus on EEG after days/weeks of onset • Risk of neurological deficits and postsurgical complications
Steroids	Potentially beneficial effects on cerebral edema and intracranial pressure	Adverse events: glucose intolerance, psychiatric disturbances, altered immune function, adrenal suppression
Immunoglobulins	May be useful for selected etiologies(autoimmune)	Adverse events: coagulation disorders, hypertension, hypersensitivity, aseptic meningitis, renal complications
Pyridoxine	No significant toxicity	• Adverse events: bradycardia, hypothermia, apnea, sensory neuropathy
Magnesium	Potential benefits in mitochondrial disease (POLG1) and magnesium deficiencies	• Adverse events (high dose): arrhythmia, neuromuscular blockage, hypotension

Aguilar CB, et al. Semin Neurol 2020

Conclusions

- Novel drugs targeting the underlying pathophysiology of SE may help improve the outcomes
- Early polytherapy may be more rational than sequential treatment in patients at risk for RSE/ SRSE
- Early awareness of potentially treatable etiology is also important
- Future directions:
  - ASMs targeting different receptors involved in the dynamic synaptic changes
  - Understanding of pharmacogenetic factors may influence the outcome

Thank you for your attention